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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/333,966	06/16/1999	GUO-LIANG YU	1488.0310005	4780

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EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1646	19

DATE MAILED: 01/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/333,966	Yu et al.
Examiner	**Art Unit**
John Ulm	1646

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Nov 21, 2001* .

2a) X This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *27-46* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *27-46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)	18) ☐ Interview Summary (PTO-413) Paper No(s).
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	19) ☐ Notice of Informal Patent Application (PTO-152)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).	20) ☐ Other:

1) Claims 27 to 46 are pending in the instant application.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) Claims 27 to 46 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for those reasons of record in section 2 of Paper Number 5 and section 5 of Paper Number 16. Applicant has traversed this rejection on the premise that it is in conflict with the decision of *In re Brana*, 51 F.3d 1560,1566, 34 USPQ2d 1436 ,1441 (Fed. Cir. 1995). Applicant's reliance on *In re Brana* is misplaced. That court decision determined that a compound which belonged to a family of compounds known to have anti-tumor activity, which is a common and well established specific and substantial utility for that family of compounds, would be reasonably expected to have anti-tumor activity in light of positive *in vitro* data with respect to that particular compound since that data has proven to be an indicator of anti-cancer activity by other members of that family. The protein of the instant invention does not belong to a family of compounds with a common well established specific and substantial utility. The utility of those members of the receptor family to which the claimed protein in the instant application belongs lies in the knowledge that they modulate a specific physiological activity in response to a specific ligand. Since the instant specification does not disclose the identity of a native ligand for the claimed

protein, a knowledge of the pathway through which that receptor transduces its signal in response to that ligand is not particularly useful.

Applicant is reminded that the instant claims are drawn to an isolated protein which is normally found in the membrane of a cell. There is certainly no evidence that the administration of the claimed protein will produce any desirable clinical effect. Contrary to Applicant's assertions, the administration of an isolated protein of the instant invention does not induce apoptosis. The instant specification only shows that the activation of DR3 within the context of the cellular membrane of a viable cell will induce apoptosis in that cell. There is no evidence of record or line of reasoning to support a conclusion that the exogenous administration of DR3 to a cell will affect that cell in any way.

Applicant urges that the claimed DR3 proteins can be employed to produce agonist antibodies and that these agonist antibodies can be employed for clinical effect. It is noted that there is not a single example of record, either in the instant specification or the art of record, of the successful administration of an agonist antibody for clinical effect. Further, the text on page 62 of the instant specification discloses that DR3 is expressed in a lymphocyte-specific manner. One can only conclude that the successful administration to an individual of an agonist antibody to DR3 would kill all of the lymphocytes in that individual. It is unclear as to the specific clinical benefit which would be received by an individual who has had all of their lymphocytes killed. It is well known in the art that the effective treatment of lymphomas invariably involves a process which selectively kills rapidly proliferating lymphocytes to the exclusion of "normal" lymphocytes.

There is no evidence that DR3 is expressed at higher levels in rapidly proliferation lymphocytes than in "normal" lymphocyte, as would be required for an agonist antibody to be effective in the treatment of a lymphoma. In fact, one would reasonably conclude that, because DR3 is a lymphocyte-specific death-domain containing receptor which is presumably involved in controlling cell proliferation, the cells in a lymphoma have lost their ability to respond to the anti-proliferative signal from an activated DR3. Therefore, one would have to conclude that the successful administration of an effective DR3 agonist antibody to an individual would result in the selective killing of "normal" lymphocytes to the exclusion of the cells in a lymphoma. The instant specification discloses no advantage to selectively killing the normal lymphocytes in an individual suffering from non-Hodgkin's lymphoma.

Applicant has asserted that the instant application, at line 18 of page 38, discloses an association between the claimed protein and follicular lymphoma. This is incorrect. The text referred to be Applicant merely recites a variety of diseases and disorders in which apoptosis plays a role. There is no **specific assertion** in the instant specification that the claimed protein plays a role in a specific disease or disorder. Because a plurality of death domain containing receptors were known in the art at the time of the instant invention, all of which induce apoptosis upon ligand activation, the disclosure by Applicant of every disease and disorder which is known to be associated with apoptosis does not constitute a specific assertion that the claimed protein is associated with a specific disease or disorder. Further, the Warzocha et al. publication (Biochem. Biophys. Res. Com. 242:376-379, 1998) does not disclose that DR3 is associated with follicular

lymphoma. This publication discloses that the isoform of DR3 identified therein as "DR3" is associated with follicular lymphoma, in some instances, to the exclusion of DR3β and this critical relationship does not appear to be disclosed in the instant specification. The discovery that DR3β was underexpressed in some follicular lymphomas required a substantial inventive contribution beyond that which is disclosed in the instant specification. Specifically, it required one to discover that DR3 and DR3β are splice variants of a common gene product and that the underexpression of DR3β is associated with some follicular lymphoma. As indicated earlier, an invention must be patentable at the time that an application is filed. Applicant can not rely upon subsequent discoveries by themselves or others to complete the invention. In addition, the second full paragraph on page 5 of the instant specification expressly teaches that the overexpression of DR3 "may be used to detect the presence of tumors" whereas Figure 2 of the Warzocha et al. publication clearly shows that the protein identified therein as "DR3β", and which is identified in the instant specification as "DR3", is actually underexpressed in lymphoma cells. Therefore, the instant specification actually taught away from this subsequently discovered utility

Applicant urges that the extracellular domain of DR3 can be employed as a ligand antagonist in a manner analogous to the extracellular domain of a TNF receptor. The fact that the extracellular domain of DR3 would be expected to as a ligand antagonist is not disputed. However, because the instant specification does not identify a ligand for DR3 one would not know what the antagonist was acting on or what clinical effects could be expected from antagonizing a DR3 ligand. As Applicant has pointed out, the role of TNF in aggravating the

symptoms of RA were known and, therefore, an artisan could anticipate that the administration of a TNF antagonist would alleviate that aggravation. No such aggravating role has been disclosed for a DR3 ligand.

5) Claims 27 to 46 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6) Claims 27 to 46 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by each of the Chinnaiyan et al. (SCIENCE 274:990-992, 08 Nov. 1996, of record) and Kitson et al. (NATURE 384:372-375, 28 Nov. 1996, of record) for those reasons if record in section 7 of Paper Number 16.

7) Applicant's arguments filed 21 November of 2001 have been fully considered but they are not persuasive.

8) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1600